REMARKS

Discussion of Amendments

The specification and claims 23 and 36 have been amended to remove an obvious typographical error. Claims 16 and 30 have been amended to further sharpen the claim language by reciting that the non-aqueous hydrophobic liquid is present in an amount such that the water-insoluble biologically active substance remains insoluble in the non-aqueous hydrophobic liquid. This concept that the drug remains insoluble in one embodiment of the invention is found throughout the specification, e.g., Example 1, at pages 23-25. New claims 39-54 have been added and are directed to embodiments of the invention. No new matter has been added.

The Office Action

The Office Action sets for the following grounds for rejection: (1) claim 16-18, 20-32 and 34-38 are rejected under 35 USC 102(a), as allegedly anticipated by WO 99/29316 (Severson et al.); (2) claims 16-18; 20-32 and 34-38 are rejected under 35 USC 102(a), as allegedly anticipated by WO 99/29300 (RTP Pharma); and (3) claims 16-27 and 30-38 are rejected under 35 USC 103(a), as allegedly unpatentable over U.S. Patent No. 5,660,858 (Parikh et al.) in view of U.S. Patent No. 5,091,187 (Haynes).

The Examiner Interview

Applicants wish to thank Examiners Sharmila Gollamudi and Michael Hartley for the courtesies extended to Xavier Pillai, one of Applicants' attorneys, during the interview held on January 22, 2003. Applicants appreciate the valuable comments received from the Examiners, and the present response has been prepared consistent with those comments.

The Presently Claimed Invention

The presently claimed invention relates to a composition and process for preparing such a composition, wherein the water-insoluble biologically active substance remains undissolved in the hydrophobic liquid. Claims 16-54 are currently pending. A complete set of pending claims is attached.

The present application contains more than one embodiment; the presently claimed invention is directed to one of such embodiments. In this embodiment, the biologically active substance remains undissolved (as particles) in the non-aqueous hydrophobic liquid.

Discussion of Rejections

Applicants respectfully traverse the rejections.

RTP Pharma and Severson et al. fail to disclose a non-aqueous hydrophobic liquid in which the biologically active substance is not soluble or is poorly soluble as required by the present claims. Indeed, RTP Pharma teaches a composition comprising the active ingredient solubilized in a carrier medium comprising at least one hydrophobic component, at least one hydrophilic component, and at least one surfactant (page 1, third full paragraph and page 4, last paragraph). Severson et al. discloses pharmaceutical compositions containing an omega-3 fatty acid and a therapeutic agent that is substantially soluble in the omega-3 fatty acid. For these reasons, the anticipation rejections over RTP Pharma and Severson et al. should be withdrawn.

Additionally, neither RTP Pharma nor Severson et al. discloses solid particles of a water-insoluble biologically active substance of a volume weighted mean particle size in the range of 0.01 to 10 micrometers as required in the present claims, since the cited references disclose dissolving the active ingredient, rather than suspending solid particles. The "particle sizes" provided by the cited references are the sizes of the liquid droplets formed upon dispersion in the aqueous medium and not the size of the solid particle of the biologically active substance as in the present claims. Thus, the compositions of RTP Pharma and Severson et al. including the dissolved active ingredient in a hydrophobic liquid are distinctly different from the compositions of the presently claimed invention.

The Office Action would fail to make a *prima facie* case for obviousness with respect to the presently claimed invention. There is no motivation to combine Parikh et al. and Haynes. Parikh et al. teaches away from the presently claimed invention. Parikh et al. is directed to pharmaceutical compositions containing a cyclosporin dissolved in a synthetic medium chain triglyceride, and is particularly directed to the use of medium chain length triglycerides and free fatty acids to enhance the solubility of the cyclosporin in the oil phase (col. 1, lines 3-7). Furthermore, Parikh et al. teaches that the oil containing the dissolved cyclosporin is added to an aqueous solution and homogenized to form an emulsion.

The presently claimed invention, in contrast to Parikh et al., relates to a composition comprising solid particles of a biologically active substance dispersed in a non-aqueous carrier system comprised of a hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble, wherein the composition self-disperses upon addition to a fluid aqueous medium. A hydrophobic liquid in which the biologically active substance is not soluble or is poorly soluble is a requirement in the presently claimed invention. In contradistinction, the

biologically active substance must be soluble in the hydrophobic liquid in Parikh et al. Furthermore, the composition of the present invention self-disperses upon addition to a fluid aqueous medium. Parikh et al. does not disclose such a composition.

Haynes also teaches away from the presently claimed invention. Haynes is directed to phospholipid-coated microcrystals of water-insoluble drugs suspended in an aqueous solution. The presently claimed invention, in contrast to Haynes, is directed to a composition including, *inter alia*, one or more hydrophilic substances that provide a self-dispersing property to the composition when the composition is added to an aqueous medium. In contradistinction, Haynes does not disclose or fairly suggest a composition including one or more hydrophilic substances that self-disperses upon addition to an aqueous medium. Haynes discloses a suspension of solid particles in an aqueous medium. Motivation to combine Parikh et al. and Haynes, if any, can come only from a hindsight reconstruction employing applicants' invention as a road map. Hindsight reconstruction is impermissible under the law. Haynes fails to suggest a composition having a spontaneous dispersing property. The composition of the present invention does not require significant energy input for dispersion. One of skill in the art would simply never be led from the teachings of Parikh et al. and Haynes to arrive at the presently claimed invention.

Even if a combination is made, the combination does not suggest to those of ordinary skill in the art the presently claimed invention. For example, the combination does not suggest a composition having a spontaneous dispersing property.

Further, the composition of the claimed invention has an unexpected and superior property, i.e., the self-dispersing property of the presently claimed invention that gives a particle size stability not realized in the suspension arguably suggested by the combination of the cited references.

In view of the foregoing, the anticipation and obviousness rejections should be withdrawn. Claims 39-54 also should not be rejected on this basis.

Petition to Correct Inventorship

This response is accompanied by a Petition to Correct Inventorship under 37 CFR 1.48(a).

Conclusion

The application is considered in good and proper form for allowance. As the response is accompanied by a RCE, the Examiner is respectfully requested to enter the amendments. If, in

the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: April 11, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PACE et al.

Application No. 09/667,328

Filed: September 21, 2000

Art Unit: 1616

Examiner: S. S. Gollamudi

For: SURFACE MODIFIED PARTICULATE COMPOSITIONS OF BIOLOGICALLY ACTIVE SUBSTANCES

AMENDMENTS TO SPECIFICATION AND CLAIMS MADE IN RESPONSE TO THE OFFICE ACTION DATED OCTOBER 16, 2002

Amendments to the paragraph beginning at page 16, line 29:

In one aspect, preferred biologically active substances members of the group consisting of an antihypertensive drug; nifedipine; and anticholinergic drug; ursodiol; a drug for treating a gastro-intestinal disorder; budesonide; an antineoplastic drug; ~~pcclitaxel~~paclitaxel; camptothecin; a derivative of ~~pcclitaxel~~paclitaxel; a derivative of camptothecin; an NSAID; piroxicam; an anti-fungal agent; itraconazole; an anti-viral agent; acyclovir; a derivative of acyclovir, a cholesterol controlling agent; fenofibrate; an ~~immuno-suppresive~~ immuno-suppressive peptide; cyclosporine; a protein used in the treatment of diabetes; insulin; and a derivative of insulin.

Amendments to existing claims:

16. (Twice Amended) A composition comprising stable solid particles of a water-insoluble biologically active substance of a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

a non-aqueous hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble~~;~~, and is present in an amount such that the water-insoluble biologically active substance remains insoluble in the non-aqueous hydrophobic liquid;

a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substances that provides a self-dispersing property to said composition,

wherein upon addition of said composition to a fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non-aqueous hydrophobic liquid containing particles of surface stabilized water-insoluble biological substance suspended in the oily droplets of the dispersion and particles of said water-insoluble biologically active substance migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

23. (Twice Amended) The composition of claim 16, wherein the biologically active substance is selected from the group consisting of nifedipine, ursodiol, budesonide, ~~pcclitaxel~~paclitaxel, camptothecin, a derivative of ~~pcclitaxel~~paclitaxel, a derivative of camptothecin~~,~~ piroxicam, itraconazole, acyclovir, a derivative of acyclovir, fenofibrate, cyclosporine, and insulin.

30. (Amended) A process for preparing a dosage form of a biologically active substance comprising adding to a fluid aqueous medium a composition comprising stable solid particles of said water-insoluble biologically active substance having a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

a non-aqueous hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble; and is present in an amount such that the water-insoluble biologically active substance remains insoluble in the non-aqueous hydrophobic liquid;

a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substance that provides a self-dispersing property to said composition,

wherein upon addition of said composition to said fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non aqueous hydrophobic liquid containing particles of said surface stabilized water-insoluble biological substance suspended in the oily droplets of the dispersion and

particles of said water-insoluble biologically active substance migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

36. (Twice Amended) The process of claim 30, wherein the biologically active substance is selected from the group consisting of nifedipine, ursodiol, budesonide, ~~pcclitaxel~~paclitaxel, a derivative of ~~pcclitaxel~~paclitaxel, camptothecin, a derivative of camptothecin, piroxicam, itraconazole, acyclovir, a derivative of acyclovir, cyclosporine, and insulin.